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Article type : Letter to Editor

Letter to the Editor

Mucous membrane pemphigoid and lichenoid reactions after immune checkpoint inhibitors: common pathomechanisms

Running head: **Pemphigoid, lichenoid reaction and immune checkpoint inhibitors**

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Funding sources: This article has no funding source
IRB approval status: Not applicable
Prior presentation: None
Manuscript word count: 609 words
References: 10
Figure: 1
Table: 1
Conflict of interest: None

Keywords: Mucous membrane pemphigoid, pemphigoid, lichen, lichenoid reaction, immune checkpoint inhibitors, anti-PD-1 antibodies, drug-triggered pemphigoid

Immune checkpoint inhibitor (ICI) therapy has demonstrated impressive antitumor activity.[1] However, it causes adverse effects, including lichenoid reactions.[1,2] Cases of ICI-triggered bullous pemphigoid (BP) and anecdotally mucous membrane pemphigoid (MMP) have also been reported. [2-6] We describe two new cases of pembrolizumab-triggered MMP, one of which was associated with cutaneous lichenoid lesions.

Case 1. A 77-year-old man presented with metastatic melanoma for which he received pembrolizumab and stereotactic radiation therapy (**Table 1**). Six months later he developed pruritic skin lesions followed by painful oral lesions. Examination revealed lichenoid papules on the limbs as well as oral erosions of the cheek mucosa and gingiva (**Fig. 1**). Light microscopy studies of skin and mucosal biopsy specimens showed a lichenoid inflammation with apoptotic basal keratinocytes and subepithelial cleft formation with eosinophils, respectively. Immunopathological studies confirmed the diagnosis of

MMP. The patient was given doxycycline and topical corticosteroids with partial remission of oral lesions, while the lichenoid lesions resolved. Five-month after ICI cessation, his condition remained unchanged.

Case 2. An 81-year-old woman was given pembrolizumab for metastatic melanoma. Six months later, she presented with painful oral lesions of the buccal and gingival mucosa as well as isolated erosions on her face and scalp (**Fig. 1**). Light microscopy studies of a buccal mucosa were consistent with MMP. Immunopathological studies were positive (**Table 1**). The patient was given doxycycline and topical corticosteroids. During the 12-month follow up, despite ICI termination, she still had relapsing oral lesions, while skin lesions resolved.

MMP is an autoimmune subepithelial blistering disorder characterized by involvement of mucosal surfaces, a tendency for scarring and a variable reactivity profile of patients' autoantibodies.[3] Skin lesions, which are found in 25% of cases, are often limited and confined to the face and scalp, as in our second patient.[3] Only three cases of MMP linked to ICI therapy have been described so far: while two cases had only mild oral involvement as in our two observations, the third case developed severe stenosis of the larynx. [4-6] Our first case was striking, since he developed oral MMP in combination with lichenoid cutaneous lesions. Lichenoid reactions with rarely mucosal involvement are observed in approximately 25% of cases during ICI therapy, but BP has also been increasingly reported. [2,5] In a review of 27 ICB-triggered BP cases, the median age was 68 years.[2,5] The interval between start of ICIs and BP onset was highly variable with a median of 6 months, as in our cases. The disease may however also occur several months after ICB discontinuation.[5]

ICI therapy with anti-programmed death-1/ programmed death-ligand 1 results in a breakdown of tolerance, reduces activity of regulatory T cells (Tregs), and activates B cells and autoreactive T cells.[1] *Murphy* mice characterized by a Tregs dysfunction develop both a lichenoid interface dermatitis and an autoantibody response to BP180 and BP230.[7] Hence, Tregs blockade may result in both autoreactive cellular and humoral response to the same antigenic targets of the epidermal and epithelial BMZ. Lichen planus (LP) patients have also been found to have an autoreactive T cells against BP180, the major target antigen of BP and MMP.[3,8] These findings may explain the

phenotype observed in our first patient showing concomitantly a cutaneous lichenoid and an oral subepithelial blistering dermatosis and further raise the question about the nosologic relationship of our first case with *lichen planus pemphigoides* as well as a new subtype of MMP with oral lichen features.[3,9] Hence, autoimmune blistering and lichenoid dermatoses, as also observed in in paraneoplastic pemphigus, seem to share an immune response directed against the same target antigens, explaining their potential clinical presentations overlap.[10] The factors responsible for the final clinical phenotypes remains to be elucidated.

Acknowledgments: The authors are thankful to Mrs M. Elias and Mrs A. von Gunten for their photography work.

Abbreviations:

ICB, immune checkpoint blockade
BP, bullous pemphigoid
MMP, mucous membrane pemphigoid
BMZ, basement membrane zone
CR, complete remission
PR, partial remission
Tregs, regulatory T cells
DIF, direct immunofluorescence microscopy
IIF, indirect immunofluorescence using NaCl-separated normal human skin

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Legend

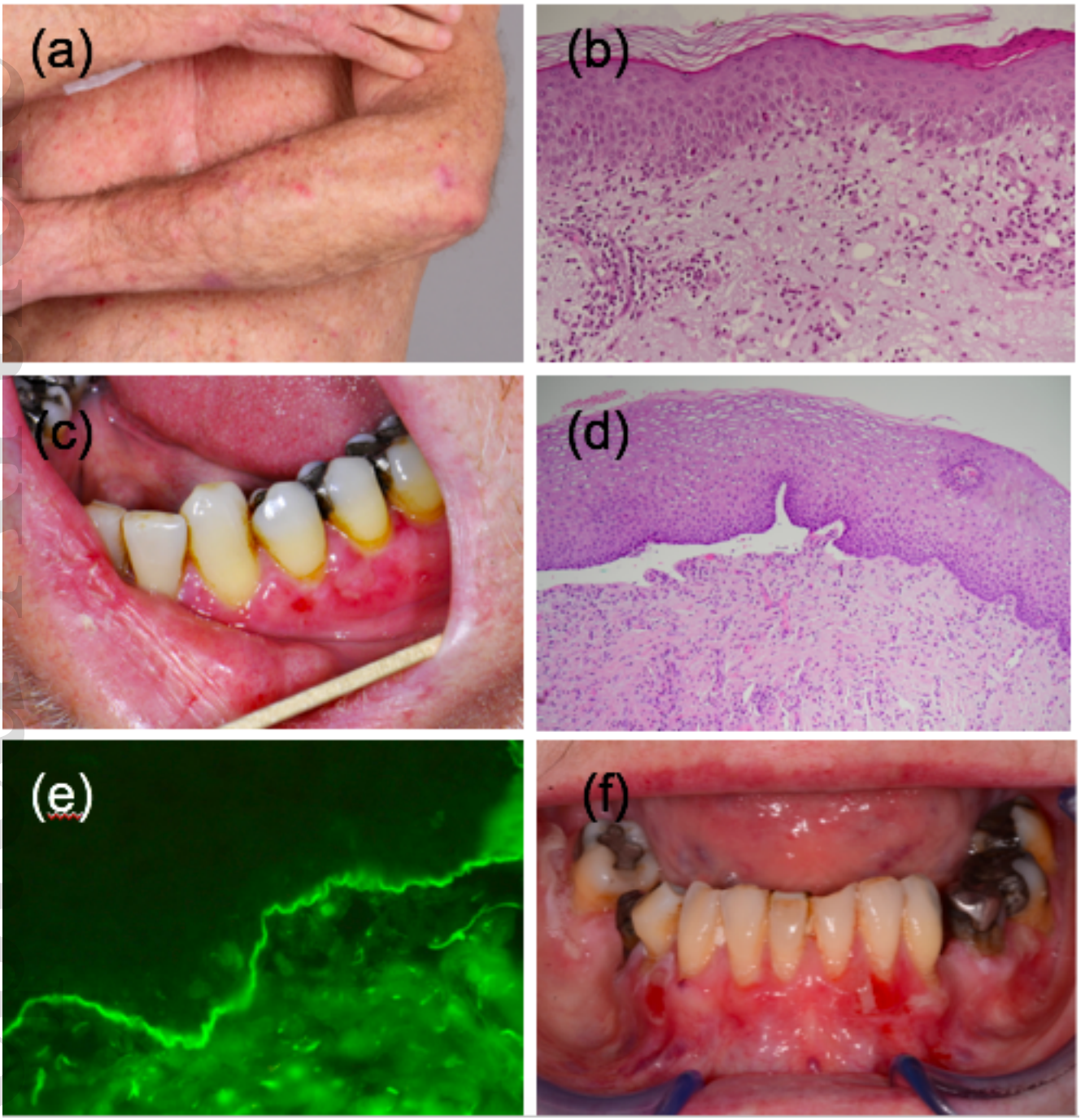
Figure 1. Clinicopathological features of the patients. Case 1 with (**a**) isolated violaceus colored lichenoid maculopapular lesions on the upper limbs. (**b**) Light microscopy studies of a skin biopsy specimen show an interface dermatitis, apoptotic keratinocytes and a lymphocytic infiltrate in the upper dermis with some eosinophils. (**c**) Erythema and erosions of the gingival margins. (**d**) Light microscopy studies of an oral biopsy specimen demonstrate subepithelial blister formation and inflammation with eosinophils. (**e**) Direct immunofluorescence microscopy shows linear IgG deposits along the epithelial basement membrane zone. Case 2 (**f**) with desquamative gingivitis with edema, erythema and erosions. Sloughing of the mucosa with shaggy margins.

Table 1. Demographics and characteristics of reported cases of mucous membrane pemphigoid (MMP) after immune checkpoint inhibitor (ICI) therapy

Patients Age, sex (reference)	**Malignancy**	**Clinical features**	**Immunopathology**	**Management of malignancy**	**Onset of MMP after starting ICI**	**Therapy and course of MMP**
62 year, male (4)	Metastatic Merkel cell carcinoma	Oral blisters and erosions (tongue, buccal mucosa) No skin involvement	Linear deposits of C3 along the epithelial BMZ ELISA-BP180, 23.6 U/mL IIF, epidermal staining IB, positive for BP180 (IgG, IgA)	Pembrolizumab, (Keytruda®), 2 mg/kg, every 3 weeks	13 weeks after initiation ICI then stopped	Oral doxycyline Topical steroids PR on therapy
83 years, Female (5)	Metastatic melanoma	Oral erosions, gingivitis,pseudo-lichenoid lesions No skin involvement	Linear deposits of IgG and C3 along the epithelial BMZ IIF studies, negative ELISA-BP180, negative ELISA-BP230, negative IIE, positive	Pembrolizumab 2 mg/kg, every 3 weeks	66 weeks (24 weeks after ICI stop)	Oral doxycyline Corticosteroid oral washes CR off therapy after three months
61 years, female (6)	Metastatic ovarian adenocarcinoma	Oral erosions and gingivitis Conjunctivitis, dysphagia, nasal and pharyngeal erosions, and laryngeal stenosis	Linear deposits of IgG and C3 along the epithelial BMZ IIF, epidermal staining	Carboplatin and Paclitaxel, then Pembrolizumab 2 mg/kg. stopped after 5 cycles (tumor progression) Start of doxorubicin	6 weeks after ICI initiation	Oral prednisone Infliximab Methylprednisolone IVIG Rituximab PR on therapy Death due to sepsis
78 years, male Case 1 *Present report*	Malignant melanoma with brain and pulmonary metastases	Pruritic cutaneous lichenoid lesions Oral cheek erosions, desquamative gingivitis	Linear deposits of IgG along the epithelial and epidermal BMZ (with n-serration pattern) ELISA-BP180, 18.3 U/ml IIF, epidermal staining	Stereotactic radiation and pembrolizumab, 2 mg/kg, every 3 for 38 cycles ICI stopped after CR of melanoma	24 weeks after initiation	Oral doxycyline Oral nicotinamide Topical corticosteroids PR on minimal therapy

82 years, female Case 2 *Present report*	Malignant melanoma with skin metastases	Oral blisters erosions of cheek mucosa, soft palate and desquamative gingivitis Single cutaneous blisters	Linear deposits of IgG /C3 along the epithelial and epidermal BMZ (with n-serration pattern) ELISA-BP180, negative ELISA-BP230, negative	Pembrolizumab 3 weeks, for 16 cycles ICI stopped after CR of melanoma	24 weeks after initiation	Oral doxycyline Corticosteroids oral washes Topical corticosteroids PR on minimal therapy

BMZ, basement membrane zone; IIF, indirect immunofluorescence microscopy using NaCl-separated normal human skin; IIE, immunoelectron microscopy; CR and PR, complete response and partial response, respectively, according to either revised RECIST criteria or outcome measures for MMP; IVIG, intravenous immunoglobulins



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